SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Mobile Bearing Total Knee Prosthesis
Device Trade Name:	*NexGen*® LPS-Flex Mobile and LPS-Mobile Bearing Knee Systems
Applicants Name/Address:	Zimmer, Inc. P.O. Box 708 1800 West Center Street Warsaw, Indiana USA 46581-0708
Premarket Approval (PMA) Number:	P060037
Date of Panel Recommendation:	None
Date of Notice of Approval to Applicant:	December 10, 2007

II. INDICATIONS FOR USE

- This device is indicated for patients with severe knee pain and disability due to:
    - Osteoarthritis,
    - Primary and secondary traumatic arthritis,
    - Avascular necrosis of the femoral condyle,
    - Moderate valgus, varus, or flexion deformities (i.e., valgus/valgus deformity of ≤15°, fixed flexion deformity of ≤10°).
- This device is intended for cemented use only.

III. CONTRAINDICATIONS

- Contraindications include:
    - Previous history of infection in the affected joint and/or local/systemic infection that may affect the prosthetic joint.
    - Insufficient bone stock on femoral or tibial surfaces.
    - Skeletal immaturity.
    - Neuropathic arthropathy.
    - Osteoporosis or any loss of musculature or neuromuscular disease that compromises the affected limb.
    - A stable, painless arthrodesis in a satisfactory functional position.
    - Severe instability secondary to the absence of collateral ligament integrity.
- Total knee arthroplasty is contraindicated in patients who have rheumatoid arthritis (RA) and an ulcer of the skin or a history of recurrent breakdown of the skin because their risk of postoperative infection is greater. RA patients using steroids may also have increased risk of infection. Late infections in RA patients have been reported 24+ months postoperative.

IV. WARNINGS and PRECAUTIONS

Please reference the *NexGen* LPS-Flex Mobile and LPS-Mobile Bearing Knee systems package insert (Instructions for Use) for Warnings and Precautions.

V. DEVICE DESCRIPTION

The *NexGen* LPS-Flex Mobile Bearing Knee and *NexGen* LPS-Mobile Bearing Knee are both semi-constrained, non-linked, posterior-stabilized, rotating platform mobile bearing total knee prostheses, which are part of the larger *NexGen* Complete Knee Solution, *Legacy* Knee – Posterior Stabilized (LPS) system. The two *NexGen* LPS Mobile Bearing Knee systems both utilize the following four main components:

- LPS femoral component*
- LPS-Mobile tibial articular surface component
- Fluted Stem Mobile tibial baseplate component
- All-Poly patella component

* The only difference between the two knee systems is in the design of the femoral components. The LPS-Flex Mobile Bearing Knee utilizes the *NexGen* LPS-Flex non-porous femoral component, whereas the LPS-Mobile Bearing Knee utilizes the *NexGen* LPS non-porous femoral component.

A complete description of all system components is provided below.

Femoral Components

The LPS-Flex and LPS femoral components are non-porous and made of cast cobalt chromium molybdenum (CoCrMo) alloy conforming to ASTM F75[1] / ISO 5832-4[2]. This alloy is referred to by the Zimmer trade name *Zimaloy*. The articulating surfaces are polished to minimize friction with the polyethylene tibial insert and patellar components. The two femoral components are available in six identical sizes (AB, C, D, E, F, and G). Both femoral components are available in left and right configurations with two inferior surface options: PMMA precoat, and non-coated (Option) surfaces, both intended for fixation with bone cement. Both femoral components are designed for use with both cruciate ligaments excised. The range of motion for the LPS-Flex femoral component is designed to range from 0° to 155° of flexion whereas the range of motion for the 'standard' LPS femoral component is designed to range from 0° to 120° of flexion. To achieve the increased flexion range, the LPS-Flex femoral component incorporates a thicker and extended posterior condyle relative to the LPS femoral component.

The LPS-Flex and LPS femoral components can both be used with the following mobile bearing *NexGen* components:

- LPS-Mobile articular surface component
- Fluted Stem Mobile tibial baseplate component

[1] ASTM International, Standard Specification for Cobalt-28 Chromium-6 Molybdenum Alloy Castings and Casting Alloy for Surgical Implants

[2] International Organization for Standardization, International Standard - Implants for Surgery, Metallic materials, Part 4: cobalt-chromium-molybdenum casting alloy

The femoral components, which both incorporate the same trochlear groove geometry, are to be used with the *NexGen* All-Poly patella components.

Neither femoral component is designed to accommodate stem extensions.

Tibial Bearing Insert

The LPS-Mobile articular surface components (tibial inserts) are made of machined, compression molded ultra-high molecular weight polyethylene (UHMWPE) conforming to ASTM F648.

The tibial inserts are available in six sizes that match to one corresponding femoral component and three tibial baseplates. For example, the size C/2-4 tibial insert matches with the size C femoral component and the size 2, 3, or 4 tibial baseplate. Each insert is available in six thicknesses (9mm, 10mm, 12mm, 14mm, 17mm, and 20mm) to facilitate ligament balancing and joint line restoration. The corresponding thickness of polyethylene under the condyles is 5.5mm, 6.5mm, 8.5mm, 10.5mm, 13.5mm, and 16.5mm, respectively. Table 1 displays the compatibility of tibial inserts with femoral and tibial baseplate components of the device system. Sizes are identical for all LPS-Flex Mobile Bearing Knee and LPS-Mobile Bearing Knee components.

Table 1. Component Compatibility for the LPS-Flex and LPS-Mobile Bearing Knees.

	Femoral Component Size					
Tibial Baseplate Size	AB	C	D	E	F	G
1	AB/1-3					
2	AB/1-3	C/2-4				
3	AB/1-3	C/2-4	D/3-5			
4		C/2-4	D/3-5	E/4-6		
5			D/3-5	E/4-6	F/5-7	
6				E/4-6	F/5-7	G/6-8
7					F/5-7	G/6-8
8						G/6-8
Patella Size	Standard size patellae are used with all LPS and LPS-Flex Femoral Components: 26mm (inset only), 29mm, 32mm, 35mm, 38mm, and 41mm					

The tibial inserts are compatible *only* with the above referenced femoral and tibial baseplate components.

The mobile bearing tibial insert rotates on the highly polished trunnion of the tibial baseplate. No anterior/posterior or medial/lateral translation is permitted by the design. Posterior and liftoff forces are counteracted by the trunnion. The 17mm and 20mm thick inserts utilize a secondary locking screw that threads into the trunnion to further resist liftoff that may occur at high flexion angles. Size 9mm to 14mm thicknesses do not require the locking screw. The locking screw is made from wrought CoCrMo alloy conforming to ASTM F1537[3].

[3] ASTM International, Standard Specification for Wrought Cobalt-28 Chromium-6 Molybdenum Alloy for Surgical Implants

Tibial Baseplate

The Fluted Stem Mobile tibial baseplate components (tibial baseplate) are made from cast CoCrMo alloy conforming to ASTM F75 / ISO 5832-4.

The tibial baseplates are available with both non-coated (Option) and PMMA precoated non-articulating surfaces. Only the PMMA precoated version accommodates stem extensions. Fixation to bone is intended by cemented use only.

The superior surface is smooth with no surrounding rim and there is a cylindrically shaped trunnion located on the anterior half along the mid-line. An anterior rail sits at the anterior edge along the mid-line. The distal stem incorporates a small delta keel where it joins with the bottom of the baseplate. The PMMA precoated version includes a female Morse-type taper within the distal stem. A threaded hole in the back of the stem allows for insertion of a locking screw that provides additional fixation to any stem extension.

Tibial baseplates are available in 8 sizes (1 – 8) to allow optimal cortical bone coverage of the prepared tibia. Baseplates, depending on size, may be compatible with up to 3 different sizes of tibial insert. For example, the size 1 baseplate is only compatible with the AB/1-3 insert, while the size 5 baseplate is compatible with the D/3-5, E/4-6, and F/5-7 inserts. See Table 1 for the complete range of tibial baseplate component compatibility.

The Fluted Stem Mobile tibial baseplate can *only* be used with the following *NexGen* components:

- LPS-Mobile tibial articular surface component
- Straight, Offset, Sharp Fluted, and Cemented Stem Extensions (PMMA pre-coated baseplate only)

The Fluted Stem Mobile tibial baseplate is *not* compatible with any other *NexGen* tibial inserts.

The tibial baseplate/insert construct is designed to permit free rotation about the tibial baseplate trunnion up to 25° of internal or external rotation (total possible rotation is 50°). The anterior rail of the tibial baseplate helps prevent further rotation and possible spin-out of the tibial insert.

The polyethylene tibial insert is captured onto the tibial baseplate trunnion and this provides secure attachment and prevents disassembly either by close fit or the secondary locking screw (17mm and 20mm thick inserts only). When a locking screw is not used, the baseplate and insert are not physically attached to one another, other than by the mating of the trunnion/hole of the baseplate and insert. The insert sits atop the baseplate (and trunnion); free to rotate up to the limits provided by the anterior rail.

Patella

The All-Poly (all-polyethylene) patellar components are made of machined, compression molded UHMWPE, conforming to ASTM F-648[4]. The UHMWPE is identical to that used for the LPS-Mobile tibial articular surface components.

[4] ASTM International, Standard Specification for Ultra-High Molecular Weight Polyethylene Powder and Fabricated Form for Surgical Implants

The articulating surface of the All-Poly patellar component is axisymmetric (round) with a flattened sombrero shape. It is intended for cemented use only. It has three grooved pegs and cement pockets on the cemented side which are designed to enhance cement fixation. The All-Poly patella is shaped to conform to the patellar sulcus (trochlear groove) of both the LPS-Flex and LPS femoral components (which both have the same trochlear groove). It is designed to provide conforming contact during normal and high flexion activities. The patella is available in six diameters, 26mm, 29mm, 32mm, 35mm, 38mm, and 41mm, which permit optimal bone coverage and surgical options. The 26mm patella is available in an inset design, only.

Other System Components

The *NexGen* stem extension components are made of wrought titanium (Ti-6Al-4V) alloy conforming to ASTM F-136[5] / ISO 5832-3[6]. This alloy is referred to by the Zimmer trade name *Tivanium*. All available sizes and versions of *NexGen* stem extensions are compatible with any *NexGen* stemmed femoral or tibial baseplate component with a female Morse-type taper, such as the PMMA precoat Fluted Stem Mobile tibial baseplate. The stem extensions are not compatible with the LPS-Flex or LPS femoral components (as these are not stemmed) nor the non-coated (Option) Fluted Stem Mobile tibial baseplate (as it has no female taper).

The stem extensions are available in straight and offset configurations and can be used with or without bone cement. Stem extensions are also available in three design versions: standard, sharp fluted, and cemented. The stem extensions are available in various lengths and diameters. Available lengths are 75mm, 105mm, 120mm, 145mm, 175mm, and 200mm. Available diameters are 10mm – 20mm in 1mm increments, 22mm, and 24mm. Not all three design versions are available in all sizes. For example, the cemented stem only comes in a 13mm diameter.

Both straight and offset stem extensions can be sized to provide optimal canal filling. The offset stem extension allows the component to be positioned 4.5mm away from the center of the canal when needed.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

- Non-surgical treatment (e.g., medications, exercise, strength training), or no treatment at all
- Arthroscopy/debridement
- Fusion of the joint
- Realignment of the joint by osteotomy
- Cartilage resurfacing/replacement treatments
- Partial knee replacement (e.g., unicondylar, hemi-, patellofemoral)
- Fixed bearing or other mobile bearing total knee replacement

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[5] ASTM International, Standard Specification for Wrought Titanium-6 Aluminum-4 Vanadium ELI (Extra Low Interstitial) Alloy (UNSR 56401) for Surgical Implant Applications

[6] International Organization for Standardization, International Standard - Implants for Surgery, Metallic materials, Part 3: Wrought titanium 6-aluminum 4-vanadium alloy

VII. MARKETING HISTORY

The LPS-Mobile tibial articular surface and the non-coated (Option) version of the Fluted Stem Mobile tibial baseplate have been marketed internationally since 1999. The PMMA precoat version of the Fluted Stem Mobile tibial baseplate was released internationally in 2000. The LPS-Mobile tibial articular surface and Fluted Stem Mobile tibial baseplate components have been sold in the European Union, Australia, India, Asia, Japan and Thailand. The device has not been withdrawn from marketing for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Serious complications may be associated with any total knee joint replacement procedure. These complications include, but are not limited to:

- Loosening of the prosthetic knee components
- Fracture/damage of the prosthetic knee components
- Removal and/or replacement of the device system or its components
- Soft tissue impingement or damage
- Dislocation and/or joint instability
- Malalignment of the prosthetic knee components
- Bone fracture
- Nerve damage
- Infection
- Swelling
- Leg length discrepancies
- Poor range of motion
- Delayed wound healing
- Temporary or permanent neuropathies
- Pain
- Cardiovascular disorders including venous thrombosis, pulmonary embolism or myocardial infarction
- Histological reactions resulting in inflammation
- Metal sensitivity
- Corrosion of metal components
- Excessive wear secondary to damage of mating wear surfaces and/or debris that can initiate osteolysis which may result in loosening of the implant
- Death

Potential adverse effects associated with mobile bearing knees such as the *NexGen* LPS-Flex Mobile Bearing Knee and *NexGen* LPS-Mobile Bearing Knee systems include:

- Excessive wear secondary to damage of multiple mating wear surfaces that can initiate osteolysis which may result in loosening of the implant
- Tibiofemoral bearing disassembly
- Tibiofemoral subluxation
- Dislocation and/or joint instability
- Knee stiffness

Any of these adverse effects may require medical or surgical intervention.

See Tables 8 and 9 for a complete listing of the adverse events reported in the study of the *NexGen* LPS-Flex Mobile Bearing Knee System.

IX. SUMMARY OF PRECLINICAL STUDIES

Laboratory Studies

The following tests were completed by the applicant based upon the device risk analysis and FDA's "Class II Special Controls Guidance Document: Knee Joint Patellofemorotibial and Femorotibial Metal/Polymer Porous-Coated Uncemented Prostheses". The testing summarized below was performed to provide support for safety and/or effectiveness of the proposed mobile components.

LPS-Mobile Articular Surface Cantilever Fatigue Test
The LPS-Mobile tibial articular surface was tested to ensure that it had sufficient strength to resist fatigue fracture when there is edge overhang of the articular surface over the edge of the tibial baseplate during extreme rotation.

Both 9mm (n=5) and 17mm (n=6) LPS-Mobile tibial articulating surfaces were tested. Cantilever tests were conducted on the articular surface to determine if the components could survive 225,000 cycles (30 deep flexion events per day over a 20-year lifetime) at a maximum load of 2669 N (600 lbs) without fracture or significant deformation.

All of the samples completed the 225,000 cycles without fracture or significant deformation, meeting the design requirements.

LPS-Mobile Articular Surface / Fluted Stem Tibial Baseplate Lift-off Test (Posterior)
This test evaluated the potential of the LPS-Mobile tibial articular surface to disassemble from the tibial baseplate trunnion.

In some activities, such as kneeling on the floor with the knee near 90° of flexion and the body center of mass directly over the articular surface spine, the loading of the articular surface can result in a net moment that would tend to raise the posterior edge of the articulating surface.

The test was designed to mimic the loading conditions anticipated in the knee when attempting to rise from kneeling on one knee, with the knee at approximately 95° of flexion. Biomechanical analysis showed that the patella tendon load is at a minimum, acting to compress the articulating surface to the tibial tray with approximately 489 N (110 lbs) of force, while the weight of the patient acts against the articulating surface spine with about 185 lbs of force. The estimated number of load cycles was based on an average of 6.8 occurrences per day for 20 years, or 50,000 cycles.

Both 14mm (n=1) and 20mm (n=5) LPS-Mobile tibial articulating surfaces were tested. The 14mm devices represent the thickest component which does not use a supplementary locking screw to assist locking stability, while the 20mm component is the thickest component which does use a locking support screw.

All samples survived 50,000 cycles without disassembly.

LPS-Mobile Articular Surface/Fluted Stem Tibial Baseplate Lift-off Test (Anterior)
This test evaluated the potential of the LPS-Mobile tibial articular surface to disassemble from the tibial baseplate trunnion in an anterior direction.

In deep flexion, the femoral component is normally thrust anteriorly, constrained by the cruciate ligaments or, in posterior stabilized total knee arthroplasties, the articulating surface spine. When thigh and calf contact occurs, the femur may shift posteriorly and load the posterior edge of the insert. A test protocol was developed to mimic this loading condition.

Each test was run with a 1334 N (300 lbs) constant load applied for 225,000 cycles (30 deep flexion events per day over a 20-year lifetime).

Both 14mm (n=5) and 20mm (n=5) LPS-Mobile tibial articulating surfaces were tested. The 14mm devices represent the thickest component that does not use a supplementary locking screw to assist locking stability, while the 20mm component is the thickest component that does use a locking support screw.

All of the samples completed 225,000 cycles without disassembly.

LPS-Mobile Articular Surface Spine Shear Test

Along with the posterior and anterior lift-off tests, the ability of the polyethylene articular surface spine to resist fracture due to high flexion loading while captured by the Fluted Stem tibial baseplate was assessed.

The peak (worst-case) spine load levels were determined at 155° flexion to be 1632 N (367 lbs). Each test was run for 225,000 cycles (30 deep flexion events per day over a 20-year lifetime).

Both 9mm (n=5) and 20mm (n=7) LPS-Mobile tibial articulating surfaces were tested. The 9mm spine presents the smallest cross section at the surface shear plane due to the post hole for the tray pivot structure, which passes completely through the 9mm articulating component. The thinner surface also reduces structural stiffness of the articulating component. The 20mm samples represent the thickest and stiffest polyethylene components. The component height also creates the greatest bending moment resisted by the locking screw.

All samples survived 225,000 cycles without fracture.

Support Screw Integrity Testing Summary

An articular surface support screw is used on 17 and 20mm thick LPS-Mobile tibial articulating surface components to provide sufficient structure for the components to resist disassembly from the Fluted Stem Mobile tibial baseplate component. A series of tests were performed to show that the screw was sufficient for its designed application. Evaluation of the surface support screw during cyclic loading was conducted in concert with the anterior lift-off, posterior lift-off, and rotary overhang fatigue tests referenced above. Five samples were evaluated in each of the three tests.

Screws were torqued to either 10.7 or 13.6 N-m (95 or 120 in-lbs). In each test, the tibial components were subjected to either 50,000 cycles (posterior lift-off) or 225,000 cycles (anterior lift-off and rotary overhang). The average torque required to remove the screws (static - no cyclic loading) was 11.0 N-m (97.5 in-lbs) for those screws assembled with a 13.6 N-m (120 in-lbs) torque. The average removal torque was 81% of the assembly torque.

The average post-fatigue torque removal values were 8.5 N-m (72 in-lbs) for the screws assembled with 10.7 N-m (95 in-lbs) of torque, and 10.2 N-m (90 in-lbs) for samples assembled with 13.6 N-m (120 in-lbs) of torque. The removal torque was 76% and 75% of the assembly torque, respectively, for the two tested groups.

There have been no reported problems of the support screw backing out or loosening in the IDE clinical study, or in international use. No screw fractures have been reported.

Femoral Contact Area Analysis

The LPS-Flex femoral component and LPS femoral component have identical condylar geometries up through 120° flexion (the designed flexion range of the LPS femoral component). Therefore, femoral/tibial contact area analysis was conducted using the LPS-Flex femoral component (designed flexion range of 155°). The contact area for the *NexGen* LPS-Flex Mobile Bearing Knee was measured using a TEKSCAN Sensor (Tekscan, Inc., South Boston, MA). The *NexGen* LPS-Flex Mobile Bearing Knee contact area was compared to the standard fixed bearing *NexGen* LPS Knee contact area.

The *NexGen* LPS-Flex Mobile Bearing Knee design showed increased contact area at 0°, 10° and 155° of flexion. Contact area differences were insignificant between 45° and 120° flexion. Increased contact area at the extreme ranges of flexion (and highest loading situations) provides for a larger area over which to distribute the loads applied to the tibial insert articular surface, theoretically reducing the stress within the polyethylene.

Patellar Deformation and Stability Test

The *NexGen* LPS-Flex Mobile Knee and *NexGen* LPS-Mobile Bearing Knee use the *NexGen* All-Polyethylene patella. The sulcus geometry of the LPS-Flex femoral knee component which supports and mates with the patella is identical to that of the LPS femoral knee component. Therefore, testing with the LPS femoral knee component was used to demonstrate deformation and lateral stability.

The patello/femoral articulation remains the same for both the fixed and mobile bearing designs of the *NexGen* LPS Knee; therefore the characterization testing of the patello/femoral interface is applicable to both designs.

Deformation testing consisted of a worst-case load of 900 lbs at the worst-case flexion angle of 105° to 115° (where the patella has the least support). Five 35mm and five 41mm patellae were evaluated. The samples showed acceptable deformation.

Patello/femoral lateral stability is a function of the depth of the femoral sulcus. The geometry of the femoral sulcus of the LPS-Flex femoral and LPS femoral components has been shown both preclinically and clinically to adequately resist lateral subluxation, with no known patello/femoral problems reported in the IDE clinical study, international use, or when used as components of a fixed bearing knee system.

Fluted Stem Tibial Baseplate Cantilever Fatigue Test

The tibial baseplate must be of sufficient strength to resist fatigue fracture. Historical data has shown that cantilever strength of 700 N (167 lbs) or more is sufficient to resist fracture.

Cantilever tests were conducted on the tibial baseplate to determine if the strength was greater than the design specification (700 N). Five size 7 baseplates were tested. Size 7 baseplates represent the worst case stress condition for the design series as it has the worst combination of moment arm and cross sectional area. Each sample was tested to 10,000,000 load cycles or until fracture. The test protocol followed the guidelines described in ASTM F1800[7]. This standard is applicable to both fixed bearing and mobile bearing knees.

[7] ASTM International, Standard Test Method for Cyclic Fatigue Testing of Metal Baseplate Components of Total Knee Joint Replacements

All five test samples completed 10,000,000 load cycles without fracture.

Constraint Evaluation

The level of constraint (resistance to motion) for the *NexGen* LPS-Flex Mobile Bearing Knee was analyzed. The tibial insert/tibial tray interface is a flat-on-flat articulation which allows complete rotational freedom within the limits defined by rigid stops. The femoral/tibial insert motion is resisted by the dished articulating surface geometry and the close conformity between the two components.

The test consisted of a computer simulation of the femoral/tibial insert interfaces using the methods outlined in ASTM F1223[8]. Anterior/posterior (A/P) shear, internal/external (I/E) rotation, and medial/lateral (M/L) shear resistance (constraint) are evaluated by this standard. Clinically relevant loads are not imparted in these tests. This simulation does not incorporate the free sliding motion between the polyethylene insert and the tibial baseplate. It is assumed that the rotational movement would occur freely until stopped by mechanical means (anterior rail). Once the movement is stopped, the simulation predicts the constraint between the femoral and polyethylene components.

The passive articular surface constraints of the *NexGen* LPS-Flex Mobile Bearing Knee design were found to be typical of semi-constrained posterior stabilized designs.

Results are merely indicative of the *relative* stability characteristics of the design, as well as factors which may adversely affect fixation stresses at the tibiofemoral bone/prosthesis interface. Ultimately, stability of a mobile bearing knee is highly dependent on the intact soft tissue structures of the knee, which in turn are dependent on surgical technique and proper patient selection criteria (indications/contraindications).

Wear Test

The *NexGen* LPS-Flex Mobile Bearing Knee was compared to a legally marketed mobile bearing knee to determine if there was a difference in cumulative wear rates. Both designs were also compared to a fixed bearing knee design tested previously in the same manner.

For the *NexGen* LPS-Flex Mobile Bearing Knee, 9mm articulating surfaces (two lots of 3; n=6) were tested (thinnest cross section = 5.5mm) and for the legally marketed mobile bearing knee, 10mm components (one lot of 2, one lot of 3; n=5) were tested (thinnest cross section = 6.0mm). Both samples represented the thinnest surfaces available (worst-case) for that device and, therefore, the most susceptible to excessive wear. The femoral and tibial baseplate sizes (size E femoral, size 4 tibial for the LPS) were selected because they were mid-range for both designs and were comparable. The LPS devices were sterilized by radiation in a nitrogen atmosphere, while the marketed mobile bearing devices were sterilized by gas plasma.

Testing was conducted in a 6-station knee wear simulator for 5 million cycles at a physiological frequency of 1.1 Hertz. During the test the tibial baseplate and femoral components were mounted with bone cement on their respective simulator fixtures, and each joint was tested in an environmentally sealed chamber in which undiluted bovine serum lubricant was recirculated and maintained at 37 ± 3° C. The serum lubricant was changed every half million cycles. Wear of the articular surfaces was determined gravimetrically by weighing them every half million cycles for the first three million cycles and every million

[8] ASTM International, Standard Test Method for Determination of Total Knee Replacement Constraint

cycles thereafter.

The Zimmer developed protocol was based on a draft of a proposed ISO standard on knee wear testing (ISO/WD [1999] 14243-3 Draft) and simulates a walking gait. The peak load was 3200 N (719 lbs) during the stance phase of gait and the minimum load was 50 N (11 lbs) during swing phase. The peak load equals 3.2 time body weight at the 95th percentile of weight for an adult American male (224 lbs).

Load-soak controls for each design were also run to correct for fluid absorption during the wear test. The load-soak controls were subjected to the same test conditions, including load, as the wear specimens, but without the motion.

Lot vs. lot and knee vs. knee comparisons were made. A significant difference was noted between each of the lots, however, because the wear values for the *NexGen* LPS-Flex Mobile Bearing Knee and marketed mobile bearing knee overlapped, there was no significant difference between the two device designs. When compared to the fixed bearing knee, both mobile bearing knees exhibited less cumulative wear.

Post-test analysis of the samples showed expected wear scarring at the femoral/tibial insert surface contact areas but no evidence of edge impingement. Both devices exhibited a burnished appearance for the articular surfaces that was consistent with lower surface roughness measurements. No pitting was observed for either of the test specimens.

Comparison of LPS-Flex Femoral and LPS Femoral Components
The LPS femoral component was not evaluated in the clinical trial. In addition, this component, except where noted, was not evaluated in any of the preclinical tests summarized above. To demonstrate that the clinical data was applicable to the LPS femoral component, the applicant provided a detailed comparison of the LPS-Flex femoral and standard LPS femoral components to demonstrate that the preclinical data (and therefore LPS-Flex clinical data) are representative of how the LPS femoral components can be expected to perform when used with components as part of the *NexGen* LPS-Mobile Bearing Knee system.

A test-by-test discussion was provided to demonstrate how the devices tested (i.e., LPS-Flex femorals) were either representative, or worst-case examples, as compared to the LPS femoral components. The applicant demonstrated that the testing provided is adequate to characterize both the LPS-Flex and LPS femoral components when used as part of the *NexGen* LPS-Flex Mobile Bearing Knee and *NexGen* LPS-Mobile Bearing Knee systems, respectively. It is noted that both femoral components are currently marketed for use with the *NexGen* LPS Fixed Bearing Knee.

Animal Studies

Beyond the biocompatibility testing recommended in ISO 10993-1[9], Zimmer did not perform any additional animal or preclinical testing relative to the biocompatibility, immunological, or toxicological aspects of the cobalt-chromium alloys, titanium alloy, or UHMWPE used for the LPS-Mobile Bearing Knee systems. These materials have a long established history of clinical use (>30 years). A summary of the ISO 10993-1 tests and results are provided in Table 2 below:

[9] International Organization for Standardization, International Standard – Biological Evaluation of Medical Devices Part 1: Evaluation and Testing

Table 2: Biocompatibility Tests and Results

Test	Result
Cytotoxicity - ISO Elution method	No evidence of cell lysis or toxicity
ISO Sensitization- Maximization method (0.9% NaCl / Cottonseed Oil)	No evidence of causing delayed dermal sensitization
Intracutaneous Reactivity (0.9% NaCl / Cottonseed Oil)	No evidence of irritation or toxicity
ISO Acute Systemic Toxicity (0.9% NaCl / Cottonseed Oil)	No evidence of systemic toxicity
Genotoxicity - Ames Mutagenicity (0.9% NaCl /DMSO)	Not mutagenic
Implantation - 30 day	Non-irritant
Hemocompatibility	Non-hemolytic
Material Mediated Pyrogen	Non-pyrogenic

Sterilization and Shelf Life Validation

The components of the proposed *NexGen* LPS-Flex Mobile Bearing Knee and *NexGen* LPS-Mobile Bearing Knee systems are sterilized by gamma irradiation. The dose range is 25-37 kGy, providing a Sterility Assurance Level (SAL) better than or equal to 10^{-6}. ANSI/AAMI/ISO 11137[10] was used to verify the minimum sterilization dose and conduct gamma radiation processing and dose mapping validations. Resterilization instructions for various methods have also been validated by the applicant.

A shelf life of eight years for UHMWPE components and ten years for all metal components was determined through a combination of real-time and accelerated aging studies. The testing conducted on the packaging materials utilized accelerated aging according to ASTM F1980[11], as a guideline. Accelerated aging tests were conducted on representative components from the Zimmer Knee Product Family, starting at time zero and carried out to five and ten years. Concurrent to the accelerated aging tests, the product was placed in real-time tests and tensile and visual data was gathered at time zero, six months, and annually through year eight. ISO 11607[12] regards accelerated aging as sufficient evidence of claimed shelf life of new packaging materials, provided the results are acceptable and the new packaging structure is undergoing a real-time test.

Packaging tests conducted include tensile, drop, and vibration testing. All of the accelerated-aged packages and all real-time aged packages, for the current knee packaging structure have shown no evidence of degradation to the packaging materials, and the packaging integrity has remained unharmed.

[10] International Organization for Standardization, International Standard - Sterilization of healthcare products - Requirements for validation and routine control - Radiation Sterilization
[11] ASTM International, Accelerated Aging of Sterile Medical Device Packages
[12] International Organization for Standardization, International Standard - Packaging for Terminally Sterilized Medical Devices

X. SUMMARY OF CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the *NexGen* LPS-Flex Mobile Bearing knee system (treatment group) to the non-mobile bearing *NexGen* LPS-Flex Fixed Bearing Knee (control group) for patients with severe knee pain and disability due to osteoarthritis in the US under IDE G000157. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical data is presented below.

Study Design

The pivotal study was an open, randomized, multi-center, concurrently controlled, non-inferiority clinical trial that compared the safety and effectiveness of the *NexGen* LPS-Flex Mobile Bearing knee system (treatment group) to the non-mobile bearing *NexGen* LPS-Flex Fixed Bearing Knee (control group) at the two year postoperative endpoint. The five individual clinical study endpoint assessments included pain, function, radiographic parameters, device survivorship, and complications.

The efficacy of the *NexGen* LPS-Flex Mobile Knee was determined by comparing the survivorship, Knee Society Assessment (pain) and Function scores, and selected radiographic parameters, of the treatment group to the control group in the primary study cohort.

The safety of the *NexGen* LPS-Flex Mobile Bearing Knee in patients was evaluated by monitoring the difference in cumulative rates of severe knee related complications and unanticipated adverse device effects (UADE's) between the treatment group and the control group in the primary study cohort.

Follow-up pain, functional and radiographic examinations were made at 6 weeks, 6 months, 12 months, and 24 months after surgery. At two year intervals thereafter, patients were evaluated until the last patient enrolled completed a two year follow-up evaluation.

Clinical Inclusion and Exclusion Criteria

Enrollment in the study was limited to patients who met the following inclusion criteria:

- Age: 21 to 80 years
- Sex: Both males and females were included, with no selection on gender.
- Weight: Patients were required to weigh less than 250 pounds at the time of enrollment with a recommended thigh/calf index of ≥ 90.
- Patients with severe knee pain and disability due to degenerative joint disease based on physical and radiographic examination, and history including:
    - Osteoarthritis (OA) or rheumatoid arthritis (RA)
    - Primary and secondary traumatic arthritis
    - Polyarthritis
    - Collagen disorders
    - Avascular necrosis of the femoral condyle or pseudogout
    - Post-traumatic arthritis
    - Varus, valgus, or flexion deformities
- Knee Society Assessment (pain) and Function scores of ≤ 60.
- Knee flexion ≥ 90 degrees.

- Preoperative radiographic evidence of joint degeneration including but not limited to decreased joint space, presence of osteophytes, and/or other significant radiographic evidence of arthritic degeneration that can not be treated in a non-operative fashion.

Patients could *not* enroll in the study if they met any of the following exclusion criteria:

- Patients with a previous history of infection in the affected joint.
- Patients with previously failed knee endoprosthesis of any kind.
- Patients presenting with a contralateral knee implant in place.
- Patients requiring bilateral knee replacement under the same anesthetic.
- Patients with Charcot joint disease or other severe neurosensory deficits.
- Patients presenting with previous patellectomy of the index knee.
- Skeletally immature individuals.
- Patients with grossly insufficient femoral or tibial bone stock, e.g., due to osteoporosis, metabolic bone disease, congenital anomaly, or previous surgery to the index joint that could affect outcome, including but not limited to high tibial osteotomy or a patient requiring bone grafting.
- Patients with loss of musculature or absence of musculoligamentous supporting structures required for appropriate soft tissue balance.
- Patient is pregnant.
- Varus or Valgus deformity >20 degrees.
- Fixed flexion deformity >15 degrees.
- Knee flexion < 90 degrees.
- Previous high tibial osteotomy.
- Previous femoral osteotomy.
- Patient is a poor compliance risk, i.e., history of ethanol or drug abuse, or mental handicap that would compromise patient compliance with respect to rehabilitation or follow-up.

Patient Selection and Randomization Procedures

All patients presenting with degenerative joint disease were screened for eligibility for participation in the clinical trial by patient history, physical examination, and radiographic views of the knee completed within 90 days of the proposed surgery. Patients with a preexisting contralateral total knee implant were not enrolled into the study. However, patients receiving a contralateral knee implant after the index surgery were allowed to remain in the study (i.e., as bilateral cases) and considered protocol deviations for purposes of the final primary safety and effectiveness analysis. Choice of contralateral implant was determined by the randomization scheme.

Randomization and enrollment occurred after patients satisfied all inclusion criteria and informed consent obtained.

Randomization was either to the treatment group or the control group. To assure balance in treatment assignments, individual permutated block randomization was provided to each of the 15 participating centers.

Primary and Secondary Endpoints

The primary study endpoints of safety and effectiveness incorporated five individual clinical endpoints consisting of the Knee Society Assessment (pain) and Function scores, complications, radiographic parameters, and survivorship at the two year time point (see Table 3). Survivorship was defined as the cumulative number of device or device component

removals and/or revisions over the first two postoperative years. The safety endpoint (i.e., complications) was defined as the cumulative number of a severe knee related complication or unanticipated adverse device events (UADE's) over the first two postoperative years.

The secondary study endpoint of clinical success was a composite measure of the primary safety and effectiveness endpoints, and was determined separately for each individual patient. To be considered a clinical success, a patient had to meet the success criteria for all five individual primary endpoints.

Table 3: Individual Patient Clinical Success Criteria

Primary Clinical Endpoints	Success Criteria
Knee Society Assessment (pain) Score	Knee Society Assessment (pain) Score ≥ 70
Knee Society Function Score	Knee Society Function Score ≥ 70
Adverse Events / Complications	Absence of Severe Knee Related AE's and UADE's
Radiographic Parameters	< 2mm Radiolucencies and < 2mm Implant Position Change
Survivorship / Revision	No component/device revision or removal

Statistical Analysis Plan

Data from all centers were subject to a comparability analysis prior to being pooled for the primary analysis of safety and effectiveness. The statistical analyses for the five primary study endpoints utilized data from unilateral cases, and excluded data from procedures performed on patients with a preoperative diagnosis of rheumatoid arthritis, compassionate use cases, and bilateral cases (separate analyses were carried out on these groups). Success rates for each of the five individual primary study endpoints were compared between the treatment and control groups and consisted of a non-inferiority analysis utilizing delta values specified in the protocol. Study success required that the proportion of treatment group patients meeting the success criteria for *each* of the five individual endpoints had to fall within the specified delta values for non-inferiority, when compared to the success rates of the control group for each endpoint (see Table 5).

For the secondary analysis of the composite measure of clinical success, the proportion of patients from the treatment group who met the success criteria for *all* five individual primary endpoints were compared to the control group. For the study device to be considered a clinical success, the delta value for non-inferiority (i.e., 10%) specified in the protocol must have been met with respect to the clinical success rate of the control device (see Table 7).

Primary Study Analysis Group

There were 208 cases initially enrolled in the treatment arm and 194 cases in the control arm, comprising a total of 402 cases. These patients comprised the "all enrolled" population. Of these, one LPS-Flex Mobile Bearing Knee and seven LPS-Flex Fixed Bearing Knee cases did not receive study devices due to contraindications at the time of surgery. Thus, there were 394 randomized and implanted cases: 207 with an LPS-Flex Mobile Bearing Knee (including 6 compassionate use cases); and 187 with an LPS-Flex Fixed Bearing Knee.

The primary analysis of safety and efficacy was originally intended to be "per protocol", as specified in the IDE study. However, approximately 25% of patients originally analyzed as "per protocol" patients did not meet the "per protocol" inclusion criteria regarding the pre-operative Knee Society assessment and function scores. Specifically, 43 treatment patients and 39 control patients did not meet the protocol inclusion/enrollment criteria of < 60 points for Knee Society assessment and function scores. Due to these high numbers of protocol deviations the "per protocol" statistical analysis could not be expected to provide reliable results based on the reduced sample size. As a result, the primary analysis was carried out on "as treated" patients, which included patients with pre-operative knee scores ≥ 60 points. As the number and percentage of patients with pre-operative knee scores ≥ 60 was very similar for both the treatment and control groups, and the number and percentage in the 60 – 69 point range was also very similar (this point range contained most of the deviations), it was considered acceptable to utilize the "as treated" patients as the primary analysis group, in lieu of the actual "per protocol" patient group.

After excluding bilateral TKAs, compassionate use cases, and rheumatoid arthritis cases, 173 randomized and implanted LPS-Flex Mobile Bearing Knees and 168 LPS-Flex Fixed Bearing Knees were included in the primary "as treated" analysis group that was used to evaluate the primary and secondary study endpoints for device safety and effectiveness.

Therefore, the primary analysis group of 173 study and 168 control knees is not "per protocol" but rather "as treated", and is referred to as such throughout this document.

Patient Accounting

Patient accountability was summarized for all study procedures using the available "as treated" endpoints dataset for the primary analyses. Randomized procedures not implanted with study devices, compassionate use procedures, bilateral procedures, and procedures with preoperative diagnoses of rheumatoid arthritis were excluded from the primary cohort of patients but included in the "all analyzable" cohort for safety analysis (i.e., *all* treated patients, for whom safety data is available).

Results from summaries of patient accountability based upon the primary "as treated" endpoints dataset are presented in Table 4. At the two year assessment, there were 5 postoperative deaths (as defined by the onset date of a complication which led to death) and 1 postoperative revision (as defined by the date of revision) that occurred in the 173 unilateral procedures receiving the LPS-Flex Mobile Bearing Knee. There were 3 postoperative deaths and no postoperative revisions in the 168 unilateral LPS-Flex Fixed Bearing Knees. Because results for primary study endpoints missing at two years and beyond were pulled forwards in the primary analysis dataset, there were 172 LPS-Flex Mobile Bearing Knees and 168 LPS-Flex Fixed Bearing Knees with expected two year clinical assessments. The numbers of procedures with all primary endpoint data available in this dataset were 172 for LPS-Flex Mobile Bearing Knees and 166 for LPS-Flex Fixed Bearing Knees. Based on the primary analysis dataset, compliance with the scheduled clinical assessment at postoperative year two was equal to 100% for the LPS-Flex Mobile Bearing Knee and 98.8% for LPS-Flex Fixed Bearing Knee.

Table 4. Patient Accountability –As Treated Endpoints Dataset

As of Database Closure	Pre-Op		6 Weeks		6 Months		1 Year		2 Years*	
	I	C	I	C	I	C	I	C	I	C
Theoretical Follow-Up	173	168	173	168	173	168	173	168	173	168
Cumulative Deaths	0	0	2	0	2	0	4	2	5	3
Cumulative Revisions	0	0	0	0	0	0	1	0	1	0

Expected Follow-Up	173	168	173	168	171	168	171	168	172	168
Actual[A] Follow-Up	171	167	165	158	161	158	155	153	172	166
Actual[A] % Follow-Up	98.8%	99.4%	95.4%	93.6%	93.6%	94.1%	90.6%	91.1%	100%	98.8%

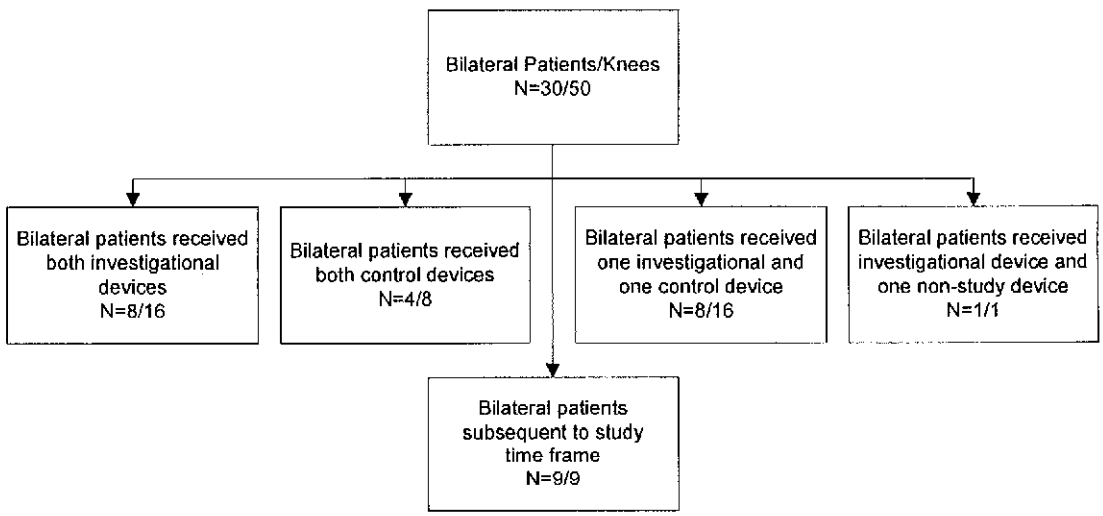
I =investigational device, C=control device

Expected = Theoretical minus deaths and revisions, unless assessed within the interval prior to death or revision.

Actual[A] = Patients with all endpoint data available.

* *The 2 Year assessment was assigned to a 2 year clinical assessment when available, a 4 year assessment when the 2 year was missing, or the last postoperative assessment when there were no clinical assessments available at 2 years or beyond. Therefore, expected follow-up at 2 years includes data from dead patients (their last postoperative assessment), and only excludes revisions.*

Thirty patients implanted with a unilateral knee eventually required a contralateral knee implant during the course of the study or after the study. During the course of the study, 21 patients received a contralateral device. Bilateral cases were subsequently removed from the primary "as treated" analysis cohort and considered as protocol deviations since bilateral devices were an exclusion criterion for this study. Bilateral cases implanted during the course of the study were analyzed separately. However bilateral patients *were* included as part of the "all analyzable" patient dataset that identified all adverse events (i.e., safety endpoint) related to total knee replacement surgery reported in the clinical study. Bilateral cases implanted during the course of the study were broken down accordingly:



Primary diagnoses of RA were observed for 6 cases in 5 patients. For these 5 patients, 3 were unilateral TKAs who received an LPS-Flex Mobile Bearing Knee. Of the remaining 2 patients, there was 1 bilateral that received both an LPS-Flex Mobile Bearing Knee and an LPS-Flex Fixed Bearing Knee, while the other received an LPS-Flex Mobile Bearing Knee and non-randomized non-study prosthesis in the contralateral knee. Rheumatoid patients were not included as part of the primary "as treated" analysis cohort, although they were part of the overall study inclusion criteria. As a result, rheumatoid patients were analyzed separately. However rheumatoid patients were included as part of the "all analyzable" patient dataset that identified all adverse events related to total knee replacement surgery reported in the clinical study.

Following the close of enrollment on June 28, 2004, six requests were made to FDA for compassionate use of the investigational device in patients originally enrolled and randomized to the treatment group, who were now presenting for contralateral total knee replacement. The patients requested, and received, the same device implanted in their contralateral knee. These patients were not included as part of the primary "as treated" analysis cohort. As a result, compassionate use patients (who were also bilateral recipients) were analyzed separately. However, these patients were included as part of the "all analyzable" patient dataset that identified all adverse events related to total knee replacement surgery reported in the clinical study.

Results

Demographic Data

Demographics were presented for the primary "as treated" dataset. Descriptive statistics were presented for key demographic variables as outlined in the clinical protocol: age; gender; operative side; preoperative diagnosis; concurrent medical history; preoperative Knee Society scores; and operative time. Results suggest that there were no significant differences in baseline, demographic, or operative variables at the alpha = 0.05 level of significance between study devices for key variables specified in the study protocol.

Analysis of Primary Safety and Efficacy Endpoints

Fifteen sites participated in the clinical study of the investigational *NexGen* LPS-Flex Mobile Bearing Knee prosthesis. This number of centers permitted assessment of the consistency of outcomes across a variety of investigators.

For the five primary study endpoints, the analyses of the "as treated" patients utilized revision and complication endpoints that were cumulative over the first two years postoperatively, while Knee Society and radiographic endpoints corresponded to the two year clinical assessment only. In the analysis of primary Knee Society and radiographic endpoints, when a two year clinical assessment was missing and a four year assessment was available, the four year assessment was pulled backwards (last observation carried backwards, or LOCB). When both two and four year assessments were missing, the last available postoperative assessment was carried forward (LOCF). The difference between treatment groups with respect to LOCB and LOCF was not significant and did not impact the study results.

The results for the individual primary efficacy and safety endpoints of pain, function, radiographic parameters, survivorship, and severe knee related adverse events at the two year study endpoint are given in Table 5.

Table 5. Primary Efficacy and Safety Endpoints Analysis – Available As Treated Endpoints

Primary Study Endpoint	LPS Flex Mobile (N=173)	Control Device (N=168)	Difference (98% CI) ¤ [δ = delta]*	Fisher's Exact Test p-value^ (Lt tail)
Knee Society Assessment (pain) Score N Mean (Std Dev) (Min, Max)	 165 87.9 (12.89) (49, 100)	 165 88.0 (14.10) (37.6, 100)	 -0.16 points (-3.64, 3.31) [-5.7 points]	

Knee Society Function Score N Mean (Std Dev) (Min, Max)	172 79.7 (22.04) (0, 100)	168 80.5 (20.38) (5, 100)	-0.80 points (-6.2, 4.5) [-8.2 points]	
Radiolucency ≥ 2mm and/or Implant Component Position Change ≥ 2mm % (n/N)	1.2% (2/172)	2.4% (4/164)	1.3% (-4.7%, 2.1%) [5.7%]	0.90[1]
Revision/Removal of Study Device or Component % (n/N)	0.6% (1/173)	0% (0/168)	0.6% (-0.8%, 1.9%) [4.1%]	0.51[2]
Severe Knee Related Complications & UADEs – % (n/N)	1.7% (3/173)	3.0% (5/168)	-1.2% (-5.1%, 2.6%) [8.9%]	0.87[3]

* *δ is the small, maximum clinically acceptable, pre-specified non-inferiority margin. A negative sign was added to the value specified in the clinical protocol to indicate the direction of the limit for interpretation.*

* *The 98% two-sided confidence limit is presented as it provides the 99% one-sided lower (upper) limit when the upper (lower) bound is ignored as required to assess non-inferiority*

1 *Since the p-value was 0.90, a value which is greater than the alpha (Type I error) level of 1 percent (0.01) pre-specified for the one-sided test of the primary radiographic endpoint, the LPS-Flex Mobile Bearing Knee does not differ from the control device with any clinical significance at 2 years.*

2 *Since the p-value was 0.51, a value which is greater than the alpha (Type I error) level of 1 percent (0.01) pre-specified for the one-sided test of the primary survival endpoint, the LPS-Flex Mobile Bearing Knee does not differ from the control device with any clinical significance at 2 years.*

3 *Since the p-value was 0.87, a value which is greater than the alpha (Type I error) level of 1 percent (p=0.01) pre-specified for the one-sided test of the primary safety endpoint, the LPS-Flex Mobile Bearing Knee does not differ from the control device with any clinical significance at 2 years.*

Primary Knee Society Assessment Score Endpoint

The LPS-Flex Mobile Bearing Knee patient cohort had an equivalent average KSS assessment (pain) score (87.9) at the study's two year endpoint to the LPS-Fixed Bearing Knee patient cohort (88.0) with a difference of only 0.1 points. Statistical analysis demonstrates no statistical difference in the mean KSS assessment score at two years. Therefore, the study device met the KSS assessment score study success criteria of non-inferiority in comparison to the control.

Primary Knee Society Function Score Endpoint

The LPS-Flex Mobile Bearing Knee had a slightly lower average KSS function score (79.7) at the study's two year endpoint than did the LPS-Fixed Bearing Knee (80.5) giving a difference of 0.8 points. This demonstrates no statistical difference in the mean KSS function

score at two years. Therefore, the study device met the KSS function score study success criteria of non-inferiority in comparison to the control.

Primary Safety Endpoint

The LPS-Flex Mobile Bearing Knee had numerically fewer severe knee related complications and unanticipated adverse device events (UADEs) at the study's two year endpoint (3) than did the LPS-Fixed Bearing Knee (5). Correspondingly, the study device also had a lower severe knee related complication rate (i.e. safety failure rate) as compared to the control (~1.7% vs. ~3.0%, respectively) giving a failure rate difference of 1.2%. Statistical analysis demonstrates no statistical difference between the two groups with respect to the cumulative incidence of severe knee related complications and UADEs at two years.

Primary Survival Endpoint

The LPS-Flex Mobile Bearing Knee cohort had one revision at two years endpoint while the control group had none (0). This demonstrates no statistical difference in the cumulative incidence of revisions and/or removals of the device components at two years. Therefore, the study device met the survivorship study success criteria of non-inferiority in comparison to the control.

Primary Radiographic Endpoint

The LPS-Flex Mobile Bearing Knee had fewer cases (2) that were radiographic failures at two years than did the LPS-Fixed Bearing Knee (4). Correspondingly, the study device also had a lower radiographic failure rate as compared to the control (~1.2% vs. ~2.4%, respectively) giving a failure rate difference of 1.3%. This demonstrates that the LPS-Flex Mobile Bearing Knee group does not differ statistically from the LPS-Flex Fixed Bearing Knee group in terms of the prevalence of radiolucencies of ≥ 2 mm and/or implant component position change ≥ 2 mm at two years. Therefore, the study device met the radiographic study success criteria of non-inferiority in comparison to the control.

Secondary Analysis of Clinical Success

A composite measure of the primary safety and effectiveness endpoints was determined separately for each individual patient. To be considered a clinical success, a patient had to meet the success criteria for *all* five primary study endpoints noted in Table 6. Table 6 displays the proportion of "as treated" patients that met the success criteria for each of the five individual primary study endpoints at two years post-operatively.

Table 6: Proportion of Patients That Met Success For Each Primary Endpoint at 2 Years

Success Criteria	LPS Flex Mobile (n= 173)	LPS Flex Fixed (n=168)
Knee Society assessment (pain) score ≥ 70	92% (152/165)	88% (145/165)
Knee Society function Score ≥ 70	79.7% (137/172)	80.5% (135/168)
Absence of severe knee related AE's and UADE's	98.3% (170/173)	97% (163/168)
< 2mm radiolucencies and < 2mm subsidence for all views	98.8% (170/172)	97.6% (160/164)
No component/device removal	99.4% (172/173)	100% (168/168)

A secondary endpoint analysis of the composite measure of clinical success was performed on the "as treated" population at two years. Table 7 displays the composite clinical success rates for the *NexGen* LPS-Flex Mobile Bearing Knee in comparison to the *NexGen* LPS-Flex Fixed Bearing Knee.

Table 7. Secondary Endpoint Analysis for Clinical Success – Available As Treated Endpoints

Secondary Study Endpoint	LPS Flex Mobile (N=173)	LPS Flex Fixed (N=168)	Difference (90% CI) [δ = delta]*
Composite Measure of Achieving Clinical Success – n/N (%)	114/165 **(69.1%)**	109/161 **(67.7%)**	1.4% (-7.1%, 9.9%) [10.0%]

* *δ is the small, maximum clinically acceptable, pre-specified non-inferiority margin. A negative sign was added to the value specified in the clinical protocol to indicate the direction of the limit for interpretation.*

¤ *The 90% two-sided confidence limit is presented as it provides the 95% one-sided upper limit when the lower bound is ignored as required to assess non-inferiority*

The LPS-Flex Mobile Bearing Knee had a greater number of cases (114) that were clinical successes at the study's two year endpoint than did the LPS-Fixed Bearing Knee (109). The study device also had a higher clinical success rate as compared to the control (69.1% vs. 67.7%, respectively) giving a success rate difference of 1.4%. Statistical analysis demonstrates no statistical difference between the study groups in the composite measure of clinical success at two years. Therefore, the study device met the secondary study success criteria of non-inferiority in comparison to the control.

Adverse Events

A complete list of the frequency and prevalence rates of all general and knee related complications identified in the clinical study of 388 cases in 374 patients (i.e., all analyzable procedures from *all* randomized and implanted cases) are listed in Table 8 and Table 9, respectively.

Table 8. General Postoperative Complication Rates* for All Analyzable Procedures

General Postoperative Complication	*LPS Flex Mobile (N=201) n (%)*	*LPS Flex Fixed (N=187) n (%)*	*Fisher's Exact Test P-value*
Anemia	17 (8.5%)	9 (4.8%)	0.16
Cardiac Arrhythmia	4 (2.0%)	5 (2.7%)	0.74
Congestive Heart Failure	0	2 (1.1%)	0.23
Death	5 (2.5%)	3 (1.6%)	0.73
Infection (contralateral knee cellulitis, following prostectomy, postop - not specified)	1 (0.5%)	2 (1.1%)	0.61
Hemathrosis	5 (2.5%)	1 (0.5%)	0.22
Ileus	2 (1.0%)	1 (0.5%)	>0.99

General Postoperative Complication	*LPS Flex Mobile (N=201) n (%)*	*LPS Flex Fixed (N=187) n (%)*	*Fisher's Exact Test P-value*
Myocardial Infarction	2 (1.0%)	0	0.50
Nerve Injury (lumbar spine issues and associated with the surgical procedure)	0	2 (1.1%)	0.23
Pulmonary Embolism	1 (0.5%)	0	>0.99
Respiratory Infection	3 (1.5%)	5 (2.7%)	0.49
Stroke	0	1 (0.5%)	0.48
Urinary Retention	1 (0.5%)	4 (2.1%)	0.20
Urinary Tract Infection	3 (1.5%)	2 (1.1%)	>0.99
Other General Complications	221 (73.4%)	197 (70.6%)	0.46

* *The prevalence rates for general complications were determined independently for each complication type as the ratio of the total number of reported complications relative to the sum of the corresponding total number of procedures without a complication plus the total number of reported complications for each type. General complications for bilateral patients were handled on a case level for each individual patient.*

Table 9. Time Course Distribution of Knee-Related Postoperative Complications and Overall Knee-Related Complication Rates* for All Analyzable Procedures

Knee-Related Postoperative Complication**	Preop		6 weeks		6 months		1 year		2 year		LPS Flex Mobile (N=201) *n (%)*	LPS Flex Fixed (N=187) *n (%)*	Fischer's Exact Test P-value
	Mobile	Fixed	Mobile	Fixed	Mobile	Fixed	Mobile	Fixed	Mobile	Fixed			
Deep Wound Infection < 6 weeks	0	0	0	1	0	0	0	0	0	0	0	1 (0.5%)	0.48
Deep Vein Thrombosis	0	0	10	9	0	1	0	0	0	0	10 (5.0%)	10 (5.3%)	>0.99
Delayed Wound Healing	0	0	1	0	0	0	0	0	0	0	1 (0.5%)	0	>0.99
Device Clicking	0	0	2	4	0	2	1	1	1	0	4 (2.0%)	7 (3.7%)	0.37
Dislocation (poly only, relocated spontaneously)	0	0	1	0	0	0	0	0	0	0	1 (0.5%)	0	>0.99
Effusion	0	0	3	7	2	2	4	1	0	3	9 (4.3%)	13 (6.9%)	0.38
Flexion Contracture	0	0	1	4	0	1	0	0	0	0	1 (0.5%)	5 (2.7%)	0.11
Fracture of Femur	0	0	0	1	0	0	0	0	0	0	0	1 (0.5%)	0.48
Fracture of Patella	0	0	1	0	0	0	0	0	0	1	1 (0.5%)	1 (0.5%)	>0.99
Hematoma	0	0	1	4	0	1	0	0	0	0	1 (0.5%)	5 (2.7%)	0.11
Heterotopic Ossification-Femur	0	0	0	0	1	0	0	0	0	0	1 (0.5%)	0	>0.99
Nerve Deficit	0	0	0	1	0	0	1	0	0	0	1 (0.5%)	1 (0.5%)	>0.99
Nerve Injury (lumbar spine[2], peroneal nerve palsy[3])	0	0	0	1	0	0	0	1	0	0	0	2 (1.1%)	0.23
Patella Clunk	0	0	0	0	0	0	0	0	0	1	0	1 (0.5%)	0.48
Patellofemoral Crepitus	0	0	0	0	0	0	0	2	0	0	0	2 (1.1%)	0.23
Patellofemoral Subluxation	0	0	0	0	1	0	0	1	0	0	1 (0.5%)	1 (0.5%)	>0.99
Stiff Knee Resulting in Manipulation 4 were done under anesthesia	0	0	14	3	0	0	0	0	0	0	14 (7.0%)	3 (1.6%)	0.01
Superficial Infection	0	0	0	4	0	0	0	0	0	0	0	4 (2.1%)	0.05
Tibial Base Plate Loosening	0	0	0	0	0	0	1	0	0	1	1 (0.5%)	1 (0.5%)	>0.99
Tibial Pain	0	0	0	0	0	0	0	0	1	0	1 (0.5%)	0	>0.99
Wound Dehiscence	0	0	1	0	0	0	0	0	0	0	1 (0.5%)	0	>0.99
Wound Drainage	0	0	3	3	0	0	0	0	0	0	3 (1.5%)	3 (1.6%)	>0.99
Other Knee Related Complications	0	2	30	26	10	15	17	12	8	10	65 (30.1%)	63 (31.7%)	0.75

* *The prevalence rates for general complications were determined independently for each complication type as the ratio of the total number of reported complications relative to the sum of the corresponding total number of procedures without a complication plus the total number of reported complications for each type.*

[2] *Unrelated to device*

[3] *Related to device*

** *Only complications reported at least once are listed here, potential complications with no reported occurrences are not listed here (e.g., femoral component loosening).*

There were a total of 748 adverse events reported. Of these complications, 386 (51.6%) involved *NexGen* LPS-Flex Mobile Bearing Knee cases, and 362 (48.4%) involved *NexGen* LPS-Flex Fixed Bearing Knee cases.

The percentages of cases experiencing at least one postoperative complication were similar between the two study device groups and did not differ statistically between the device groups, except for knee stiffness requiring manipulation, as detailed below.

General Complications

Prevalence rates for general complications did not significantly differ for any specific type. The most prevalent general complication was the "other" category, which consisted of relatively minor miscellaneous events not captured in Table 8. Although the percentages reporting a general complication type of "other" were elevated (LPS-Flex Mobile Bearing Knee 73.4%, LPS-Flex Fixed Bearing Knee 70.6%), the difference between the prevalence rates for the two study device types was not statistically significant.

Anemia was the second most prevalent complication of the general complication types. However, the difference was not statistically significant. Other specific complications classified as general were less prevalent, with rates below 3% in both study device groups.

Knee-Related Complications

The most prevalent knee-related complication was the "other" category, which consisted of relatively minor miscellaneous events not captured in Table 9. Although the percentages reporting a knee-related complication of type "other" were approximately 30%, the difference in the prevalence rates for the treatment and control groups was not significant.

Knee stiffness resulting in an intervention with manipulation differed in prevalence statistically between the LPS-Flex Mobile Bearing Knee group (7.0%) and the LPS-Flex Fixed Bearing Knee group (1.6%). It occurred 14 times in the treatment group and 3 times in the control group. This complication was the second most prevalent specific type of knee related complication. Stiffness resulting in manipulation was reported by 9 of 28 (32%) study investigators who had implanted treatment and control devices. Of the 17 cases requiring manipulation, 7 (41%) were submitted by a single investigator. This investigator's practice included prophylactic manipulation early in a patient's recovery to decrease their recovery time. Of the remaining 8 investigators who reported knee stiffness resulting in manipulation, there were no more than 2 reports by any single investigator.

Effusion and deep vein thrombosis were also adverse events that occurred with relatively high prevalence rates, as might be expected for these surgical procedures. However, the differences in rates between the two device groups were not significant.

The between-group difference in prevalence rates for superficial infection neared statistical significance. Superficial infection was more prevalent in the LPS-Flex Fixed Bearing Knee group (2.1%) and absent in the LPS-Flex Mobile Bearing Knee group (0.0%). All superficial infections occurred in the first 6 weeks postoperatively. These complications were restricted to 2 investigators, accounting for 17 percent and 11 percent of their LPS-Flex Fixed Bearing Knee cases, respectively.

Device Failures

The analysis of time to revision or removal of any study device or device component was performed using the all analyzable procedures dataset as described above. Estimates of survival (e.g., event-free) were obtained for each study device via the Kaplan-Meier method. The Kaplan-Meier survival estimate at each scheduled postoperative assessment is presented in Table 10.

Table 10. Kaplan Meier Survival Estimates and 95% Confidence Intervals for Freedom From Revision of a Study Device or Device Component for All Analyzable Procedures

Follow-up Interval	Study Device	N Events	N At Risk	K-M Survival Estimate	95% CI
6 Weeks	LPS-Flex Fixed Bearing Knee	0	187	1.0	(1.0,1.0)
	LPS-Flex Mobile Bearing Knee	0	201	1.0	(1.0,1.0)
6 Months	LPS-Flex Fixed Bearing Knee	0	187	1.0	(1.0,1.0)
	LPS-Flex Mobile Bearing Knee	0	201	1.0	(1.0,1.0)
1 Year	LPS-Flex Fixed Bearing Knee	0	187	1.0	(1.0,1.0)
	LPS-Flex Mobile Bearing Knee	0	198	1.0	(1.0,1.0)
2 Years	LPS-Flex Fixed Bearing Knee	0	184	1.0	(1.0,1.0)
	LPS-Flex Mobile Bearing Knee	1	196	0.99	(0.98,1.0)

Comparisons between study device groups were made using the log-rank non-parametric test procedure.

There were a total of 2 devices that required revision (i.e., failures) during the postoperative period of this study. One *NexGen* LPS-Flex Mobile Bearing Knee in a unilateral patient was revised during the 1 – 2 year postoperative period due to femoral component loosening. This revision was included in primary study endpoint analyses. The other revision was of a single *NexGen* LPS-Flex Fixed Bearing Knee in a bilateral patient who had multiple complications reported over the duration of the study, and was revised due to "leg pain, right calf swollen and tender". The revision was performed after the two year anniversary of device implantation. This revision was not included in the primary endpoint analyses because the patient had bilateral treatment and the revision

occurred beyond the two year study endpoint. No statistical difference in failure rates was noted between the two groups out through two years.

Bilateral, Rheumatoid Arthritis, and Compassionate Use Patients

Bilateral patients were analyzed separately due to the potential for confounding effects of the contralateral knee. Results for the five primary endpoints revealed no significant statistical difference between the treatment *NexGen* LPS-Flex Mobile Bearing Knee and the control *NexGen* LPS-Flex Fixed Bearing Knee, whether a patient received one of each knee device or two (of either system).

Rheumatoid arthritis patients were also analyzed separately from the primary "as treated" dataset. Results for the five primary endpoints revealed no significant statistical difference between those patients receiving the treatment *NexGen* LPS-Flex Mobile Bearing Knee and those receiving the control *NexGen* LPS-Flex Fixed Bearing Knee.

Compassionate use patients were also analyzed separately. Results for the five primary endpoints revealed no significant statistical differences between this group and those patients in the primary "as treated" dataset who received the treatment and control devices.

There were no revisions reported in any of these cohorts at the two year study endpoint. Results for these three patient populations were comparable to the primary "as treated" population cohort.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

The preclinical and clinical data provides reasonable assurance that the *NexGen* LPS-Flex Mobile Bearing Knee and *NexGen* LPS-Mobile Bearing Knee are safe and effective for total knee replacement for rehabilitating knees damaged as a result of noninflammatory degenerative joint disease (NIDJD) such as osteoarthritis, avascular necrosis, traumatic arthritis, and moderate valgus, varus, or flexion deformities.

Safety

The applicant provided a complete device description and thorough preclinical testing information to support device safety.

In the clinical study, the occurrence of loosening of implant components was rare. There was one revision of the *NexGen* LPS-Flex Mobile Bearing Knee for tibial baseplate loosening. The report was from a single complication with mild severity which resolved with the revision of the component. There was also a single revision in a control patient who had bilateral *NexGen* LPS-Flex Fixed Bearing Knee implants. The revision was performed beyond the two year anniversary of study device implantation.

Primary safety comparisons of cumulative rates of revision of a device or device components and prevalence of severe knee related complications and unanticipated adverse device effects (UADEs) over the first two postoperative years indicates the *NexGen* LPS-Flex Mobile Bearing Knee did not differ with any clinical significance from the *NexGen* LPS-Flex Fixed Bearing Knee.

Effectiveness

Primary effectiveness comparison of the cumulative rates of patient success for primary radiographic, pain and functional parameters at two years from the date of surgery indicate the *NexGen* LPS-Flex Mobile Bearing Knee did not differ with any clinical significance from the *NexGen* LPS-Flex Fixed Bearing Knee.

Secondary comparison of a cumulative composite safety and effectiveness measure of clinical success did not differ with any statistical or clinical significance between the *NexGen* LPS-Flex Mobile Bearing Knee and *NexGen* LPS-Flex Fixed Bearing Knee.

XII. PANEL RECOMMENDATIONS

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA application was not referred to the Orthopedic and Restorative Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH DECISION

The preclinical and clinical data of this submission constitute valid scientific evidence as defined by 21 CFR 860.7. The results obtained from the preclinical testing and clinical study provides a reasonable assurance that the *NexGen* LPS-Flex Mobile Bearing Knee and LPS-Mobile Bearing Knee are safe and effective for the indicated population. Therefore, CDRH believes that it is reasonable to conclude that the benefits of the use of the *NexGen* LPS-Flex Mobile Bearing Knee and *NexGen* LPS-Mobile Bearing Knee for the target population outweigh the risk of the illness or injury when used in accordance with the directions for use.

The conditions of approval require that a postapproval study be conducted. The conditions of approval cited in the approval order are described below.

> The applicant will perform a 10-year PAS to evaluate the longer-term safety and effectiveness of the LPS-Flex Mobile Bearing Knee. The PAS will consist of approximately 120 patients from the investigational device exemption (IDE) study arm (Group 1), as well as approximately 100 patients who are eligible for a total knee replacement and have been chosen to receive the LPS-Flex Mobile Knee (Group 2). Group 1 patients will be enrolled into a long-term study of 10 years. Group 1 patients will be evaluated postoperatively at 4, 5, 6, 8, and 10 years. Group 2 patients will be enrolled into a short term study of 5 years. Group 2 patients will be evaluated postoperatively at 6 weeks, 6 months, 1, 2, 3, 4, and 5 years. All patients from each group are to be followed for the full duration of that study group. At each time point, data on pain, function, range of motion, deformity, radiographic parameters, and health status will be collected. In addition, the applicant will collect all adverse events, including a description of the adverse event, onset date, treatment, and outcome. In the event of a revision, devices returned to Zimmer will be analyzed and a summary report of all detailed explant reports will be provided to FDA. This information will be provided in an interim status report to the FDA every six months for the first two years of the study and then in postapproval study reports on an annual basis, thereafter, until submission of a final study report. The results of this long-term data must be reflected in the labeling (via supplement) when the PAS is completed, as well as any other time point deemed necessary by FDA if significantly new information from this study becomes available.

In addition, the applicant agrees to continue working with the review team (led by Epidemiologist from the Office of Surveillance and Biometrics (OSB) at CDRH) to address the unresolved issues of the PAS protocol and finalize it.

The applicant's manufacturing facility was inspected and was found to be in compliance with the device Quality System Regulation (21 CFR 820).

CDRH issued an approval order to Zimmer on December 10, 2007.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the device labeling.

Postapproval Requirements and Restrictions: See approval order.